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# Optic Nerve Head Infiltration in Acute Leukemia in Children: An Indication for Emergency Optic Nerve Radiation Therapy

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Two pediatric patients with acute leukemia who developed optic nerve head leukemic infiltration are presented. In one patient both eyes were involved at diagnosis as well as her central nervous system. Despite systemic and intrathecal chemotherapy she lost her vision within a few weeks. Cranial irradiation at that point could not reverse this outcome. In the second patient optic nerve head infiltration was found a few months after diagnosis, treated promptly with cranial irradiation and her vision was saved. Her central nervous system (CNS) was not involved at any time.

It is stressed that ocular complaints including eye pain or blurred vision in the pediatric patient with leukemia should be investigated without delay by an ophthalmologist. In the young child these complaints may be absent and change in the visual behavior should then alert the pediatric oncologist for possible ocular problems. If optic nerve head leukemic infiltration is diagnosed and promptly treated with emergency radiation, vision can be salvaged.



**Key words:** leukemic infiltration optic nerve heads, radiotherapy of optic nerve head leukemic infiltration

## INTRODUCTION

Historically approximately 9% of children with acute lymphoblastic leukemia develop leukemic ophthalmopathy [1]. The ocular findings described are retinal hemorrhages, exudates, neovascularization, retinal microaneurysms, papilledema, optic atrophy and ocular infiltration [1–3]. We have treated two children with acute leukemia who developed optic nerve head hypertrophy as a proband manifestation of leukemic infiltration.

It has been suggested that the frequency of optic nerve head infiltration by leukemia has declined due to the increased intensity of chemotherapy [4]. These two patients are described to alert pediatric oncologists of this treatable complication. If diagnosed and promptly treated vision can be salvaged.

## PATIENTS AND METHODS

### Case 1

S.W. was three years old at diagnosis with presentation of anemia and hepatosplenomegaly. Ocular examination revealed swelling of both optic nerve heads due to leukemic infiltration with scanty scattered hemorrhages (Table I). Diagnosis of ALL with central nervous system (CNS) involvement was made. The patient was entered onto the low risk/standard ALL protocol of the Children's Cancer Group (CCG) #1881. The induction consisted of oral prednisone 40 mg/m$^2$ daily; i.v. VCR 1.5 mg/m$^2$ once weekly for four weeks; i.m. L'asparaginase 6,000 u/m$^2$ × 9; and i.t. methotrexate 12 mg once weekly × 4 starting Day 0. Craniospinal irradiation was to be given during consolidation. Six days after diagnosis visual acuity was found to be within normal range for both eyes.

The CSF after one week of treatment showed nucleated cells less than 1 × 10$^9$/L with rare blasts seen on cytopsin. No blasts were seen in subsequent CSF examination.

Two weeks following diagnosis she started to stumble into objects and her gait became unsteady. These symptoms were progressive over the next few days. Her fundi showed bilateral optic disc swelling and pallor with narrowing of the retinal arteries and engorgement of the retinal veins. No nerve fibre swelling was seen. She was designated legally blind. Neurological examination was otherwise within normal limits.

CT of her head with special attention to the orbits and optic tracts showed no abnormality. EEG was normal except for lack of response to photic stimulation. Visual

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TABLE I. Case 1: Patient S.W.

| | Laboratory data |
|---|---|
| WBC | $8.84 \times 10^9$/L |
| Hb | 83 g/L |
| Plt | $20 \times 10^9$/L |
| Blasts | $3,300 \times 10^9$/L |
| Bone marrow | Acute lymphoblastic leukemia |
| Immunophenotyping | Strong positivity for CD19, CD10, TdT |
| Morphology | $L_1 = 91\%$ |
| Cytogenetics | Hyperdiploidy with consistent aneuploidy |
| Lumbar puncture | $270 \times 10^9$/L nucleated cells |
| | On cytospin 100% were blasts |

TABLE II. Case 2: Patient J.G.

| | Laboratory data |
|---|---|
| WBC | $2.5 \times 10^9$/L |
| Hb | 45 g/L |
| Plts | $13 \times 10^9$/L |
| Blasts | $0.500 \times 10^9$/L |
| Coagulation studies | Normal |
| Bone marrow aspirate | Acute nonlymphoblastic leukemia (ANLL) |
| FAB classification | M0 with 83% blasts |
| Cytogenetic studies | Numerous abnormalities in structure and number of chromosomes |
| CSF | Normal |

evoked potentials test was severely abnormal with no response to binocular flash stimulation. Myelin basic protein in CSF was <1 ng/ml (radioimmunoassay). The clinical assumption was made that vision loss was due to optic nerve head infiltration and craniospinal irradiation was commenced immediately. She was given 1,878 cGy in eleven fractions over 2.5 weeks to include the brain, meninges and orbits + 600 cGy in three fractions to the spinal column.

Repeat visual assessment during irradiation showed resolution of the optic nerve head swelling but the vision remained absent. Bone marrow aspirate on Day 28 of induction indicated remission. She remains in complete remission 1.5 years on maintenance and legally blind.

### Case 2

J.G. is a 14.5-year-old girl who presented in December 1992 with pancytopenia and purpura. Physical examination was normal except for pallor and few bruises on the skin (Table II). She was entered onto CCG 2891 standard protocol for ANLL and randomized to receive the intensive arm that included two cycles of daunomycin, Ara-C, VP16, 6TG, dexamethasone and intrathecal Ara-C but failed to achieve remission. She was commenced on the more intensive CCG #0922 protocol that included idarubicin, fludarabine, and Ara-C. Two weeks later she started to complain of right eye pain and somewhat blurred vision.

Ocular examination revealed optic nerve head infiltration in the right eye. The left eye was normal. CSF examination and CT of the head were normal. She underwent emergency irradiation that encompassed the meninges, posterior orbit and optic nerve. She received 1,800 cGy in 10 fractions over two weeks. Her visual symptoms and ocular findings cleared within a week. Subsequent bone marrow aspirate indicated <5% blasts. She was given further cycle on the induction therapy and underwent a bone marrow transplantation with matched unrelated donor. Vision has been maintained and the ocular findings did not recur.

## DISCUSSION

In a large study of 657 children with acute leukemia published in 1976, Ridgeway et al. [1] found that 9.4% (52 children) developed leukemic ophthalmopathy at some stage of their disease. These children were treated by single agent chemotherapy with no prophylactic CNS treatment. Twenty-nine patients had ocular infiltration which included the optic nerve, retina, iris or orbit. Nine of the 29 patients had optic nerve involvement. CSF involvement was present before or at the time of the ocular abnormalities in the majority of these patients.

Review of the literature reveals other children with acute leukemia who were found to have optic nerve infiltration present at diagnosis as in our first patient [5], during the course of their treatment [2] or after coming off treatment [6,7]. In these later children optic nerve head infiltration was the only site of initial relapse. Both eyes or only one may be involved as seen in the two patients described above.

The clinical presentation of optic nerve infiltration may include decreased vision, blurred vision, and eye pain [1]. These complaints may not be verbalized in a small child as in the first patient when the ataxic gait was attributed to vincristine neurotoxicity and bone pain. It was the progression of her symptoms and the mother's comment that her child was not looking at her that other explanations for her symptoms were sought. Optic nerve head infiltration is occasionally found on routine examination without any ocular complaints [1,2,7].

The association of blasts in the CSF and optic nerve involvement, as seen in the Ridgeway et al. study [1] and our first patient, is not seen in all patients. Our second patient as well as others had clear CSF, before or at the time of the optic nerve involvement [1,2,6,7].

Venous pulsation may still be present at an early stage of the leukemic infiltration of the optic nerve. With the progression of the infiltration the optic nerve head looks pale, opaque and swollen with distended veins and compromised arterial circulation. Necrosis and destruction of the optic nerve tissue in the prelaminar area due to ischemia results in irreversible loss of vision [1,2,7].

It is important to note that the differential diagnosis of visual loss in a child with acute leukemia should include other causes. These include optic atrophy due to vincristine [8,9] or fludarabine [10], possible optic neuropathy from combination of chemotherapy and radiation [11,12] or just radiation retinopathy [13]. Transient cortical blindness secondary to vincristine has also been described [14].

Fludarabine was used in the second patient. Fludarabine has been shown to have a predilection for the optic nerve toxicity. Autopsy reports have described demyelination, vacuolization and axonal swelling. Episodes of visual disturbances occurred in this patient on several occasions following the administration of the fludarabine. The specific ocular findings and the visual disturbance as we described were compatible with optic nerve head infiltration and were not the findings of neurotoxicity described following fludarabine treatment [10].

Optic nerve involvement as evident in the two patients represents a visual emergency. Treatment should be instituted before irreversible optic nerve damage occurs. Once blindness occurs radiation may improve the appearance of the fundi but may not restore vision. Radiation that involves the posterior poles of the globes with or without whole brain treatment may still improve the vision that is impaired but not yet lost [2,15]. Combination of radiation and intrathecal chemotherapy and continuing systemic chemotherapy is the most appropriate treatment strategy [2,7]. The most important component of therapy is the irradiation. As described in the first patient, she lost her vision despite weekly intrathecal chemotherapy and systemic chemotherapy. In the second patient, the optic nerve swelling appeared following intensive systemic chemotherapy. Is the eye a pharmacologic sanctuary as suggested previously [1]? Decrease of optic nerve infiltration was observed in a patient following systemic chemotherapy before introduction of radiation [6]. The optic nerve head, like the testes in males, is probably an area where extramedullary leukemic infiltration can be easily detected clinically.

Any leukemic patient with ocular complaints should have the fundi and visual acuity evaluated immediately. Both our patients were examined by the same experienced pediatric ophthalmologist. In every child with CNS involvement, an eye examination should be undertaken. CT of the head as described in this report and others [9] did not help to support the diagnosis. MRI may prove to be better. CSF examination should be done when optic nerve head swelling is found. It may be normal as seen in the second patient and others [2,7]. If infiltration of the optic nerve head is found, prompt irradiation to the orbit and optic nerves should be given. It is likely that the quick institution of craniospinal radiation and intrathecal chemotherapy in our second patient had a major role in preventing further visual deterioration.

The chances of detecting isolated nonsymptomatic optic nerve involvement in a routine examination during treatment is probably low. In a recent review of 40 consecutive children with ALL, no optic nerve involvement was seen at diagnosis or at follow-up during treatment [16].

Loss of vision is unlikely to occur suddenly but will be gradual. A change in the visual behavior may give the important clues as to the quality of the visual function in the young child who is nonverbal. This would be an indication for prompt evaluation.

## CONCLUSION

Children with acute leukemia who present with ocular complaints should have an immediate ophthalmological assessment. If optic nerve head swelling is found, then a serious threat to their vision may be present if the swelling is due to leukemic infiltration. Prompt irradiation should be given to prevent irreversible visual loss.

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